

Jules Hoffmann and Bruce Beutler

2007 Balzan Prize for Innate Immunity

For their discovery of the genetic mechanisms responsible for innate immunity. They have worked in close cooperation to develop a new vision of the molecular defence strategy deployed by animals across a wide evolutionary spectrum against infectious agents. Their work has led to very promising medical applications.

Endogenous Activators of Inflammation in Insects and Mammals Centre International de Recherche aux Frontières de la Chimie The Scripps Research Institute in La Jolla

Adviser for the General Balzan Committee: Nicole Le Douarin

The second half of the Balzan Prize to Jules Hoffmann and Bruce Beutler is being used for joint efforts regarding the establishment of a model of inflammation in insects and mammals. The parallel study on inflammation in the absence of germs in the fruit fly (*Drosophila*) and in mice could lead to the future discovery of the causes by which, in humans, antibodies of endogenous origin are also activated in the absence of the pathogenic germs they are supposed to fight, thus producing autoimmune diseases. The two Prizewinners hired young researchers and supervised research work in their respective laboratories, which will lead to a comparative analysis of the IMD (fly) and TNF-TLR (mouse) proinflammatory, signalling pathways in infection and development. In the Beutler laboratory, the studies of Drs. Michael Berger, Sungyong Won, Lei Sun, Carrie Arnold, Amanda Blasius, Oren Milstein, and Philippe Krebs have been supported. In the Hoffmann laboratory, the work of Dr. Hidehori Fukuyama and of Dr. Anne Kaukinnen has been supported.

In La Jolla, Dr. Michael Berger has screened peptidomimetic libraries for activators of TLR signalling. These studies, designed to identify molecules that could cause unconventional activation of TLR signalling, have been performed as a collaboration with the laboratory of Professor Dale Boger at The Scripps Research Institute. Dr. Oren Milstein searched for immune activating functions of peptides that do not exist in the mouse proteome. Dr. Philippe Krebs has studied mutations that cause inflammatory disease, and their attenuation by mutations that disrupt TLR signalling. Particularly significant has been his demonstration that signalling via TLRs drives the lethal inflammatory disorder observed in mice with deficiency of the inositol polyphosphate 5

phosphatase, SHIP-1. Drs. Sungyong Won and Lei Sun have worked jointly to develop a technique for cloning mice from fibroblasts, with the goal of screening these cells en masse for ex vivo phenotypes (including spontaneous inflammatory phenotypes) before regenerating mice from them and positionally cloning the causative mutations. Dr. Carrie Arnold initiated a screen for defects in the adaptive immune response, and has been very successful with it, identifying eleven mutations to date. Dr. Amanda Blasius identified a key molecule for the responses of plasmacytoid dendritic cells to nucleic acids.

In Strasbourg, Dr. Hidehiro Fukuyama has pursued a biochemical strategy to identify proteins that interact with components of the IMD pathway in *Drosophila* to limit inflammation caused by endogenous stimuli. Dr. Kaukinnen has made a functional analysis of some of the proteins isolated by Dr. Fukuyama and has namely addressed their potential roles in activating antimicrobial peptide gene expression following stimulation by a bacterial pathogen. Exciting new data obtained over the last few weeks now point to a significant role of the IMD signaling pathway (IMD stands for immune-deficiency, this pathway is equivalent to that downstream of mammalian TNF) in the defense of flies against several viral pathogens. The Balzan funds which are still available in Dr. Hoffmann's group will be concentrated on developing this new line of research.

Publication plans: Several relevant publications are being prepared in both the Beutler and Hoffmann laboratories.

Statement by the Prizewinners: *It will be used for joint efforts regarding the establishment of a model of inflammation in insects and mammals.* Jules Hoffmann and Bruce Beutler (2007)